Guidelines: Post-resuscitation care

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1. The guidelines

The process used to produce the Resuscitation Council UK Guidelines 2015 has been accredited by the National Institute for Health and Care Excellence. The guidelines process includes:

• Systematic reviews with grading of the quality of evidence and strength of recommendations. This led to the 2015 International Liaison Committee on Resuscitation (ILCOR) Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. 1,2

• The involvement of stakeholders from around the world including members of the public and cardiac arrest survivors.

• Details of the guidelines development process can be found in the Resuscitation Council UK Guidelines Development Process Manual.

• These Resuscitation Council UK Guidelines have been peer reviewed by the Executive Committee of Resuscitation Council UK, which comprises 25 individuals and includes lay representation and representation of the key stakeholder groups.

2. Summary of changes in post-resuscitation care since the 2010 Guidelines
This section is new to the Resuscitation Council UK Guidelines; in 2010 the topic was incorporated into the section on Advanced life support.

The most important changes in post-resuscitation care since 2010 include:

- There is a greater emphasis on the need for urgent coronary catheterisation and percutaneous coronary intervention (PCI) following out-of-hospital cardiac arrest of likely cardiac cause.
- Targeted temperature management remains important but the target temperature can be in the range of 32°C to 36°C according to local policy. There was a preference for 36°C among the guidelines group because it is easier to implement and there is no evidence that it is inferior to 33°C.
- Prognostication is now undertaken using a multimodal strategy and there is emphasis on allowing sufficient time for neurological recovery and to enable sedatives to be cleared.

3. Introduction

Successful return of spontaneous circulation (ROSC) is the first step towards the goal of complete recovery from cardiac arrest. The complex pathophysiological processes that occur following whole body ischaemia during cardiac arrest and the subsequent reperfusion response during CPR and following successful resuscitation have been termed the post-cardiac arrest syndrome. Depending on the cause of the arrest, and the severity of the post-cardiac arrest syndrome, many patients will require multiple organ support and the treatment they receive during this post-resuscitation period influences significantly the overall outcome and particularly the quality of neurological recovery. The post-resuscitation phase starts at the location where ROSC is achieved but, once stabilised, the patient is transferred to the most appropriate high-care area (e.g. emergency room, cardiac catheterisation laboratory or intensive care unit (ICU) for continued diagnosis, monitoring and treatment. The post-resuscitation care algorithm (Figure 1) outlines some of the key interventions required to optimise outcome for these patients.

Of those comatose patients admitted to ICUs after cardiac arrest, as many as 40–50% survive to be discharged from hospital depending on the cause of arrest, system and quality of care. Of the patients who survive to hospital discharge, the vast majority have a good neurological outcome although many have subtle
cognitive impairment.5-8

Caption: Figure 1. Post-resuscitation care algorithm

4. The post-cardiac arrest syndrome
The post-cardiac arrest syndrome comprises:

- post-cardiac arrest brain injury
- post-cardiac arrest myocardial dysfunction
- systemic ischaemia/reperfusion response
- persistent precipitating pathology.

The severity of this syndrome will vary with the duration and cause of cardiac arrest. It may not occur at all if the cardiac arrest is brief. Post-cardiac arrest brain injury manifests as coma, seizures, myoclonus, varying degrees of neurocognitive dysfunction and brain death. Among patients surviving to ICU admission but subsequently dying in-hospital, brain injury is the cause of death in approximately two thirds after out-of-hospital cardiac arrest and approximately 25% after in-hospital cardiac arrest. Cardiovascular failure accounts for most deaths in the first three days, while brain injury accounts for most of the later deaths. Withdrawal of life-sustaining therapy (WLST) is the most frequent cause of death (approximately 50%) in patients with a prognosticated bad outcome, emphasising the importance of the prognostication plan (see below). Post-cardiac arrest brain injury may be exacerbated by microcirculatory failure, impaired autoregulation, hypotension, hypercarbia, hypoxaemia, hyperoxaemia, pyrexia, hypoglycaemia, hyperglycaemia and seizures. Significant myocardial dysfunction is common after cardiac arrest but typically starts to recover by 2–3 days, although full recovery may take significantly longer. The whole body ischaemia/reperfusion of cardiac arrest activates immune and coagulation pathways contributing to multiple organ failure and increasing the risk of infection. Thus, the post-cardiac arrest syndrome has many features in common with sepsis, including intravascular volume depletion, vasodilation, endothelial injury and abnormalities of the microcirculation.

5. Airway and breathing

Control of oxygenation

Patients who have had a brief period of cardiac arrest responding immediately to appropriate treatment may achieve an immediate return of normal cerebral function. These patients do not require tracheal intubation and ventilation but should be given with oxygen via a facemask if their arterial blood oxygen saturation is less than 94%. Hypoxaemia and hypercarbia both increase the
likelihood of a further cardiac arrest and may contribute to secondary brain injury. Several animal studies indicate that hyperoxaemia early after ROSC causes oxidative stress and harms post-ischaemic neurones. A meta-analysis of 14 observational studies showed significant heterogeneity across studies, with some studies showing that hyperoxaemia is associated with a worse neurological outcome and other failing to show this association.

The animal studies showing a relationship between hyperoxia and worse neurological outcome after cardiac arrest have generally evaluated the effect of hyperoxia in the first hour after ROSC. There are significant practical challenges with the titration of inspired oxygen concentration immediately after ROSC, particularly in the out-of-hospital setting. It may be difficult to obtain reliable arterial blood oxygen saturation values using pulse oximetry in this setting. A recent study of air versus supplemental oxygen in ST-elevation myocardial infarction (STEMI) showed that supplemental oxygen therapy increased myocardial injury, recurrent myocardial infarction and major cardiac arrhythmia and was associated with larger infarct size at six months.

Given the evidence of harm after myocardial infarction and the possibility of increased neurological injury after cardiac arrest, as soon as arterial blood oxygen saturation can be monitored reliably (by blood gas analysis and/or pulse oximetry), titrate the inspired oxygen concentration to maintain the arterial blood oxygen saturation in the range of 94–98%. Avoid hypoxaemia, which is also harmful – ensure reliable measurement of arterial oxygen saturation before reducing the inspired oxygen concentration.

**Control of ventilation**

Consider tracheal intubation, sedation and controlled ventilation in any patient with obtunded cerebral function. Ensure the tracheal tube is positioned correctly, well above the carina. Hypocarbia causes cerebral vasoconstriction and a decreased cerebral blood flow. After cardiac arrest, hypocapnia induced by hyperventilation causes cerebral ischaemia. Observational studies using cardiac arrest registries document an association between hypocapnia and poor neurological outcome. Two observational studies have documented an association with mild hypercapnia and better neurological outcome among post-cardiac arrest patients in the ICU. Until prospective data are available, it is reasonable to adjust ventilation to achieve normocarbia and to monitor this using the end-tidal CO₂ and arterial blood gas values. Although protective lung ventilation strategies have not been studied specifically in post-cardiac arrest.
patients, given that these patients develop a marked inflammatory response, it seems rational to apply protective lung ventilation: tidal volume 6–8 mL kg\(^{-1}\) ideal body weight and positive end expiratory pressure 4–8 cm H\(_2\)O.\(^{15,25}\)

Insert a gastric tube to decompress the stomach; gastric distension caused by mouth-to-mouth or bag-mask ventilation will splint the diaphragm and impair ventilation. Give adequate doses of sedative, which will reduce oxygen consumption. A sedation protocol is highly recommended. Bolus doses of a neuromuscular blocking drug may be required, particularly if using targeted temperature management (TTM) (see below). Limited evidence shows that short-term infusion (≤48 h) of short-acting neuromuscular blocking drugs given to reduce patient-ventilator dysynchrony and risk of barotrauma in patients with acute respiratory distress syndrome (ARDS) is not associated with an increased risk of ICU-acquired weakness and may improve outcome in these patients.\(^{26}\)

There are some data suggesting that continuous neuromuscular blockade is associated with decreased mortality in post-cardiac arrest patients;\(^{27}\) however, infusions of neuromuscular blocking drugs interfere with clinical examination and may mask seizures. Continuous electroencephalography (EEG) is recommended to detect seizures in these patients, especially when neuromuscular blockade is used.\(^{28}\)
Obtain a chest radiograph to check the position of the tracheal tube, gastric tube and central venous lines, assess for pulmonary oedema, and detect complications from CPR such as a pneumothorax associated with rib fractures.\(^{29,30}\)

6. Circulation

Coronary reperfusion

Acute coronary syndrome (ACS) is a frequent cause of out-of-hospital cardiac arrest (OHCA): in a recent meta-analysis, the prevalence of an acute coronary artery lesion ranged from 59%–71% in OHCA patients without an obvious non-cardiac aetiology.\(^{31}\) Many observational studies have shown that emergent cardiac catheterisation laboratory evaluation, including early percutaneous coronary intervention (PCI), is feasible in patients with ROSC after cardiac arrest.\(^{32-34}\) The invasive management (i.e. early coronary angiography followed by immediate PCI if deemed necessary) of these patients, particularly those having prolonged resuscitation and nonspecific ECG changes, has been controversial because of the lack of high-quality evidence and significant implications on use
of resources (including transfer of patients to PCI centres).

**Percutaneous coronary intervention following ROSC with ST-elevation**

In patients with ST segment elevation (STE) or left bundle branch block (LBBB) on the post-ROSC electrocardiogram (ECG) more than 80% will have an acute coronary lesion.\(^{35}\) There are no randomised studies but given that many observational studies reported increased survival and neurologically favourable outcome, it is highly probable that early invasive management is beneficial in STE patients.\(^{36}\) Immediate angiography and PCI when indicated should be performed in resuscitated OHCA patients whose initial ECG shows ST-elevation, even if they remain comatose and ventilated.\(^{37,38}\) The National Institute for Health and Care Excellence (NICE) Clinical Guideline 167 for the acute management of STEMI recommends: ‘Do not use level of consciousness after cardiac arrest caused by suspected acute STEMI to determine whether a person is eligible for coronary angiography (with follow-on primary PCI if indicated)’.\(^{39}\) This recommendation is based on low quality evidence from selected populations. Observational studies also indicate that optimal outcomes after OHCA are achieved with a combination of TTM and PCI, which can be included in a standardised post-cardiac arrest protocol as part of an overall strategy to improve neurologically intact survival.\(^{40}\)

**Percutaneous coronary intervention following ROSC without ST-elevation**
In contrast to the usual presentation of ACS in non-cardiac arrest patients, the standard tools to assess coronary ischaemia in cardiac arrest patients are less accurate. The sensitivity and specificity of the usual clinical data, ECG and biomarkers to predict an acute coronary artery occlusion as the cause of OHCA are unclear.\textsuperscript{41-44} Several large observational series showed that absence of STE may also be associated with ACS in patients with ROSC following OHCA.\textsuperscript{45-48} In these non-STE patients, there are conflicting data from observational studies on the potential benefit of emergent cardiac catheterisation laboratory evaluation.\textsuperscript{47,49,50} It is reasonable to discuss and consider emergent cardiac catheterisation laboratory evaluation after ROSC in patients with the highest risk of a coronary cause for their cardiac arrest. Factors such as patient age, duration of CPR, haemodynamic instability, presenting cardiac rhythm, neurological status upon hospital arrival, and perceived likelihood of cardiac aetiology can influence the decision to undertake the intervention in the acute phase or to delay it until later in the hospital stay.

**Indications and timing of computed tomography (CT) scanning**

Cardiac causes of OHCA have been extensively studied in the last few decades; conversely, little is known about non-cardiac causes. Early identification of a respiratory or neurological cause can be achieved by performing a brain and chest CT scan at hospital admission, before or after coronary angiography. In the absence of signs or symptoms suggesting a neurological or respiratory cause (e.g. headache, seizures or neurological deficits for neurological causes, shortness of breath or documented hypoxaemia in patients suffering from a known and worsening respiratory disease) or if there is clinical or ECG evidence of myocardial ischaemia, undertake coronary angiography first, followed by CT scan in the absence of causative lesions.\textsuperscript{51,52}

**Haemodynamic management**

Post-resuscitation myocardial dysfunction causes haemodynamic instability, which manifests as hypotension, low cardiac index and arrhythmias.\textsuperscript{12,53} Perform early echocardiography in all patients in order to detect and quantify the degree of myocardial dysfunction. Post-resuscitation myocardial dysfunction often requires inotropic support, at least transiently. The systematic inflammatory response that occurs frequently in post-cardiac arrest patients may cause vasoplegia and severe vasodilation.\textsuperscript{12} Thus, noradrenaline, with or without dobutamine, and fluid is usually the most effective treatment. The controlled
infusion of relatively large volumes of fluid is tolerated remarkably well by patients with post-cardiac arrest syndrome.

Treatment may be guided by blood pressure, heart rate, urine output, rate of plasma lactate clearance, and central venous oxygen saturation. Serial echocardiography may also be used, especially in haemodynamically unstable patients. In the ICU an arterial line for continuous blood pressure monitoring is essential. Cardiac output monitoring may help to guide treatment in haemodynamically unstable patients but there is no evidence that its use affects outcome. Some centres still advocate use of an intra-aortic balloon pump (IABP) in patients with cardiogenic shock, although the IABP-SHOCK II Trial failed to show that use of the IABP improved 30-day mortality in patients with myocardial infarction and cardiogenic shock.\textsuperscript{54,55}

A bundle of therapies, including a specific blood pressure target, has been proposed as a treatment strategy after cardiac arrest.\textsuperscript{56} However its influence on clinical outcome is not firmly established and optimal targets for mean arterial pressure and/or systolic arterial pressure remain unknown. In the absence of definitive data, target the mean arterial blood pressure to achieve an adequate urine output (1 mL kg\textsuperscript{-1} h\textsuperscript{-1}) and normal or decreasing plasma lactate values, taking into consideration the patient’s normal blood pressure, the cause of the arrest and the severity of any myocardial dysfunction.\textsuperscript{4}

During mild induced hypothermia the normal physiological response is bradycardia. Recent retrospective studies have shown that bradycardia is associated with a good outcome.\textsuperscript{57,58} As long as blood pressure, lactate and urine output are sufficient, a bradycardia of ≤40 min\textsuperscript{-1} may be left untreated. Importantly, oxygen requirements during mild induced hypothermia are reduced.

Immediately after a cardiac arrest there is typically a period of hyperkalaemia. Subsequent endogenous catecholamine release and correction of metabolic and respiratory acidosis promotes intracellular transportation of potassium, causing hypokalaemia. Hypokalaemia may predispose to ventricular arrhythmias. Give potassium to maintain the serum potassium concentration between 4.0 and 4.5 mmol L\textsuperscript{-1}.

\textbf{Implantable cardioverter defibrillators}

Consider insertion of an implantable cardioverter defibrillator (ICD) in ischaemic patients with significant left ventricular dysfunction, who have been resuscitated from a ventricular arrhythmia that occurred later than 24–48 h after a primary coronary event.\textsuperscript{59} ICDs may also reduce mortality in cardiac arrest survivors at
risk of sudden death from structural heart diseases or inherited cardiomyopathies.\textsuperscript{2}

7. Disability (optimising neurological recovery)

In the headers below, you'll find information on disability, and optimising neurological recovery.

Cerebral perfusion

Animal studies show that immediately after ROSC there is a short period of multifocal cerebral no-reflow followed by transient global cerebral hyperaemia lasting 15–30 min.\textsuperscript{60} This is followed by up to 24 h of cerebral hypoperfusion while the cerebral metabolic rate of oxygen gradually recovers. After asphyxial cardiac arrest, brain oedema may occur transiently after ROSC but it is rarely associated with clinically relevant increases in intracranial pressure.\textsuperscript{61} In many patients, autoregulation of cerebral blood flow is impaired (absent or right-shifted) for some time after cardiac arrest, which means that cerebral perfusion varies with cerebral perfusion pressure instead of being linked to neuronal activity.\textsuperscript{62} In one study autoregulation was disturbed in 35\% of post-cardiac arrest patients and the majority of these had been hypertensive before their cardiac arrest;\textsuperscript{63} this tends to support the recommendation made in the 2010 ERC Guidelines: after ROSC, maintain mean arterial pressure near the patient’s normal level.\textsuperscript{64}

Sedation

Although it has been common practice to sedate and ventilate patients for at least 24 h after ROSC, there are no high-level data to support a defined period of ventilation, sedation and neuromuscular blockade after cardiac arrest. Patients need to be sedated adequately during treatment with TTM, and the duration of sedation and ventilation is therefore influenced by this treatment. A combination of opioids and hypnotics is usually used. Short-acting drugs (e.g. propofol, alfentanil, remifentanil) will enable more reliable and earlier neurological assessment and prognostication (see prognostication below).\textsuperscript{65} Adequate sedation will reduce oxygen consumption. Use of published sedation scales for monitoring these patients (e.g. the Richmond or Ramsay Scales) may be helpful.
Control of seizures

Seizures are common after cardiac arrest and occur in approximately one-third of patients who remain comatose after ROSC. Myoclonus is most common and occurs in 18–25%, the remainder having focal or generalised tonic-clonic seizures or a combination of seizure types. Clinical seizures, including myoclonus may or may not be of epileptic origin. Other motor manifestations could be mistaken for seizures and there are several types of myoclonus, the majority being non-epileptic. Use intermittent electroencephalography (EEG) to detect epileptic activity in patients with clinical seizure manifestations. Consider continuous EEG to monitor patients with a diagnosed status epilepticus and effects of treatment.

In comatose cardiac arrest patients, EEG commonly detects epileptiform activity: post-anoxic status epilepticus was detected in 23–31% of patients using continuous EEG-monitoring. Patients with electrographic status epilepticus may or may not have clinically detectable seizure manifestations that may be masked by sedation. Whether systematic detection and treatment of electrographic epileptic activity improves patient outcome is not known.

Seizures may increase the cerebral metabolic rate and have the potential to exacerbate brain injury caused by cardiac arrest: treat with sodium valproate, levetiracetam, phenytoin, benzodiazepines, propofol, or a barbiturate. Myoclonus can be particularly difficult to treat; phenytoin is often ineffective. Propofol is effective to suppress post-anoxic myoclonus. Clonazepam, sodium valproate and levetiracetam are antimyoclonic drugs that may be effective in post-anoxic myoclonus. Routine seizure prophylaxis in post-cardiac arrest patients is not recommended because of the risk of adverse effects and the poor response to anti-epileptic drugs among patients with clinical and electrographic seizures.

Myoclonus and electrographic seizure activity, including status epilepticus, are related to a poor prognosis but individual patients may survive with a good outcome (see prognostication). Prolonged observation may be necessary after treatment of seizures with sedatives, which will decrease the reliability of a clinical examination.
**Glucose control**

There is a strong association between high blood glucose after resuscitation from cardiac arrest and poor neurological outcome.\(^{78,79}\) A large randomised trial of intensive glucose control (4.5–6.0 mmol L\(^{-1}\)) versus conventional glucose control (10 mmol L\(^{-1}\) or less) in general ICU patients reported increased 90-day mortality in patients treated with intensive glucose control.\(^{80,81}\) Severe hypoglycaemia is associated with increased mortality in critically ill patients,\(^82\) and comatose patients are at particular risk from unrecognised hypoglycaemia. Irrespective of the target range, variability in glucose values is associated with mortality.\(^83\) Compared with normothermia, mild induced hypothermia is associated with higher blood glucose values, increased blood glucose variability and greater insulin requirements.\(^84\) Increased blood glucose variability is associated with increased mortality and unfavourable neurological outcome after cardiac arrest.\(^78,84\) Based on the available data, following ROSC maintain the blood glucose at \(\leq 10\) mmol L\(^{-1}\) and avoid hypoglycaemia.\(^85\) Do not implement strict glucose control in adult patients with ROSC after cardiac arrest because it increases the risk of hypoglycaemia.

**Temperature control**

**Treatment of hyperpyrexia**

A period of hyperthermia (hyperpyrexia) is common in the first 48 h after cardiac arrest.\(^86\) Several studies document an association between post-cardiac arrest pyrexia and poor outcomes.\(^87\) The development of hyperthermia after a period of mild induced hypothermia (rebound hyperthermia) is associated with increased mortality and worse neurological outcome.\(^88,89\) There are no randomised controlled trials evaluating the effect of treatment of pyrexia (defined as \(\geq 37.6\) °C) compared to no temperature control in patients after cardiac arrest and the elevated temperature may only be an effect of a more severely injured brain. Although the effect of elevated temperature on outcome is not proven, it seems reasonable to treat hyperthermia occurring after cardiac arrest with antipyretics and to consider active cooling in unconscious patients.

**Targeted temperature management**
Animal and human data indicate that mild induced hypothermia is neuroprotective and improves outcome after a period of global cerebral hypoxia-ischaemia. Cooling suppresses many of the pathways leading to delayed cell death, including apoptosis (programmed cell death). Hypothermia decreases the cerebral metabolic rate for oxygen (CMRO$_2$) by about 6% for each 1°C reduction in core temperature and this may reduce the release of excitatory amino acids and free radicals. Hypothermia blocks the intracellular consequences of excitotoxin exposure (high calcium and glutamate concentrations) and reduces the inflammatory response associated with the post-cardiac arrest syndrome.

All studies of post-cardiac arrest mild induced hypothermia have included only patients in coma. One randomised trial and a pseudo-randomised trial demonstrated improved neurological outcome at hospital discharge or at six months in comatose patients after out-of-hospital VF cardiac arrest. Cooling was initiated within minutes to hours after ROSC and a temperature range of 32–34°C was maintained for 12–24 h. In the Targeted Temperature Management (TTM) trial, 950 all-rhythm OHCA patients were randomised to 36 h of temperature control (comprising 28 h at the target temperature followed by slow rewarn) at either 33°C or 36°C. There was no difference in mortality and detailed neurological outcome at 6 months was also similar. Importantly, patients in both arms of this trial had their temperature well controlled so that fever was prevented in both groups.

The optimal duration for mild induced hypothermia and TTM is unknown although it is currently most commonly used for 24 h. Previous trials treated patients with 12–28 h of targeted temperature management. Two observational trials found no difference in mortality or poor neurological outcome with 24 h compared with 72 h of hypothermia. The TTM trial provided strict normothermia (<37.5°C) after hypothermia until 72 h after ROSC.

The term targeted temperature management or temperature control is now preferred over the previous term therapeutic hypothermia. The Advanced Life Support Task Force of the International Liaison Committee on Resuscitation (ILCOR) made several treatment recommendations on targeted temperature management:

- Maintain a constant, target temperature between 32°C and 36°C for those patients in whom temperature control is used.
- TTM is recommended for adults after OHCA with an initial shockable rhythm who remain unresponsive after ROSC.
• TTM is suggested for adults after OHCA with an initial non-shockable rhythm who remain unresponsive after ROSC.
• TTM is suggested for adults after IHCA with any initial rhythm who remain unresponsive after ROSC.
• If targeted temperature management is used, it is suggested that the duration is at least 24 h.

Following the TTM trial, many intensive care clinicians in the UK have elected to use 36°C as the target temperature for post cardiac arrest temperature control. This has several advantages compared with a target temperature of 33°C:

• There is a reduced need for vasopressor support.
• Lactate values are lower (the clinical significance of this is unclear).
• The rewarming phase is shorter.
• There is reduced risk or rebound hyperthermia after rewarming.

**How to control temperature**

The practical application of TTM is divided into three phases: induction, maintenance and rewarming. External and/or internal cooling techniques can be used to initiate and maintain TTM.

Animal data indicate that earlier cooling after ROSC produces better outcome but this has yet to be demonstrated in humans. External and/or internal cooling techniques can be used to initiate cooling. If a lower target temperature (e.g. 33°C) is chosen, an infusion of 30 mL kg\(^{-1}\) of 4°C saline or Hartmann’s solution will decrease core temperature by approximately 1.0–1.5°C and is probably safe in a well-monitored environment. Prehospital cooling using this technique is not recommended because there is some evidence of increased risk of pulmonary oedema and re-arrest during transport to hospital.

Methods of inducing and/or maintaining TTM include:

• Simple ice packs and/or wet towels are inexpensive; however, these methods may be more time consuming for nursing staff, may result in greater temperature fluctuations, and do not enable controlled rewarming. Ice cold fluids alone cannot be used to maintain hypothermia, but even the addition of simple ice packs may control the temperature adequately.
• Cooling blankets or pads.
• Water or air circulating blankets.
• Water circulating gel-coated pads.
• Transnasal evaporative cooling – this technique enables cooling before ROSC and is undergoing further investigation in a large multicentre randomised controlled trial.  

• Intravascular heat exchanger, placed usually in the femoral or subclavian veins.  

• Extracorporeal circulation (e.g. cardiopulmonary bypass, ECMO).  

In most cases, it is easy to cool patients initially after ROSC because the temperature normally decreases within this first hour. Admission temperature after OHCA is usually between 35°C–36°C and in a recent large trial the median temperature was 35.3°C. If a target temperature of 36°C is chosen allow a slow passive rewarm to 36°C. If a target temperature of 33°C is chosen, initial cooling is facilitated by neuromuscular blockade and sedation, which will prevent shivering. Magnesium sulfate, a naturally occurring N-methyl-D-aspartate (NMDA) receptor antagonist, that reduces the shivering threshold slightly, can also be given to reduce the shivering threshold. 

In the maintenance phase, a cooling method with effective temperature monitoring that avoids temperature fluctuations is preferred. This is best achieved with external or internal cooling devices that include continuous temperature feedback to achieve a set target temperature. The temperature is typically monitored from a thermistor placed in the bladder and/or oesophagus. As yet, there are no data indicating that any specific cooling technique increases survival when compared with any other cooling technique; however, internal devices enable more precise temperature control compared with external techniques. 

Plasma electrolyte concentrations, effective intravascular volume and metabolic rate can change rapidly during rewarming, as they do during cooling. Rebound hyperthermia is associated with worse neurological outcome. Thus, rewarming should be achieved slowly: the optimal rate is not known, but the consensus is currently about 0.25–0.5°C of rewarming per hour. Choosing a strategy of 36°C will reduce this risk. 

**Physiological effects and complications of hypothermia** 

The well-recognised physiological effects of hypothermia need to be managed carefully: 

• Shivering will increase metabolic and heat production, thus reducing cooling rates - strategies to reduce shivering are discussed above. The occurrence
of shivering in cardiac arrest survivors who undergo mild induced hypothermia is associated with a good neurological outcome;\textsuperscript{111,112} it is a sign of a normal physiological response. Occurrence of shivering was similar at a target temperature of 33°C and 36°C.\textsuperscript{92} A sedation protocol is required.

- Mild induced hypothermia increases systemic vascular resistance and causes arrhythmias (usually bradycardia),\textsuperscript{113} Importantly, the bradycardia caused by mild induced hypothermia may be beneficial (similar to the effect achieved by beta-blockers); it reduces diastolic dysfunction\textsuperscript{114} and its occurrence has been associated with good neurological outcome.\textsuperscript{57,58}
- Mild induced hypothermia causes a diuresis and electrolyte abnormalities such as hypophosphataemia, hypokalaemia, hypomagnesaemia and hypocalcaemia.\textsuperscript{92,95,115}
- Hypothermia decreases insulin sensitivity and insulin secretion, and causes hyperglycaemia,\textsuperscript{91} which will need treatment with insulin (see glucose control).
- Mild induced hypothermia impairs coagulation and may increase bleeding, although this effect seems to be negligible\textsuperscript{116} and has not been confirmed in clinical studies.\textsuperscript{90,92,117} In one registry study, an increased rate of minor bleeding occurred with the combination of coronary angiography and mild induced hypothermia, but this combination of interventions was the also the best predictor of good outcome.\textsuperscript{118}
- Hypothermia can impair the immune system and increase infection rates.\textsuperscript{95,119,120} Mild induced hypothermia is associated with an increased incidence of pneumonia;\textsuperscript{121,122} however, this seems to have no impact on outcome. Although prophylactic antibiotic treatment has not been studied prospectively, in an observational study, use of prophylactic antibiotics was associated with a reduced incidence of pneumonia.\textsuperscript{123} In another observational study of 138 patients admitted to ICU after OHCA, early use of antibiotics was associated with improved survival.\textsuperscript{124}
- The serum amylase concentration is commonly increased during hypothermia but the significance of this unclear.
- The clearance of sedative drugs and neuromuscular blockers is reduced by up to 30% at a core temperature of 34°C.\textsuperscript{125} Clearance of sedative and other drugs will be closer to normal at a temperature closer to 37.0°C.

**Contraindications to hypothermia**

Generally recognised contraindications to TTM at 33°C, but which are not applied universally, include: severe systemic infection and pre-existing medical coagulopathy (fibrinolytic therapy is not a contraindication to mild induced
hypothermia). Two observational studies documented a positive inotropic effect from mild induced hypothermia in patients in cardiogenic shock\(^1\)\(^2\),\(^1\)\(^2\) but in the TTM study there was no difference in mortality among patients with mild shock on admission who were treated with a target temperature of 33°C compared with 36°C.\(^1\)\(^2\) Animal data also indicate improved contractile function with mild induced hypothermia probably because of increased Ca\(^{2+}\) sensitivity.\(^1\)\(^2\)

8. Prognostication

This section summarises the Advisory Statement on Neurological Prognostication in comatose survivors of cardiac arrest,\(^1\)\(^3\) written by members of the ERC ALS Working Group and of the Trauma and Emergency Medicine (TEM) Section of the European Society of Intensive Care Medicine (ESICM). For more detail and comprehensive referencing, see the European Advisory Statement.

Hypoxic-ischaemic brain injury is common after resuscitation from cardiac arrest.\(^1\)\(^3\) Two thirds of those dying after admission to ICU following OHCA die from neurological injury.\(^9\)\(^1\)\(^1\) Most of these deaths are due to active withdrawal of life sustaining treatment (WLST) based on prognostication of a poor neurological outcome.\(^9\)\(^1\)\(^1\) For this reason, when dealing with patients who are comatose after resuscitation from cardiac arrest, minimising the risk of a falsely pessimistic prediction is essential. Ideally, when predicting a poor outcome these tests should have 100% specificity or zero false positive rate (FPR), (i.e. no individuals should have a ‘good’ long-term outcome if predicted to have a poor outcome).\(^1\)\(^3\)\(^2\)\(^1\)\(^3\) However, most prognostication studies include so few patients that it is very difficult to be completely confident in the results. Moreover, many studies are confounded by self-fulfilling prophecy, which is a bias occurring when the treating physicians are not blinded to the results of the outcome predictor and use it to make a decision on WLST. Finally, both TTM itself and sedatives or neuromuscular blocking drugs used to maintain it may potentially interfere with prognostication tests, especially those based on clinical examination.\(^7\)\(^7\)

Prognostication of the comatose post-cardiac arrest patient should be multimodal (involve multiple types of tests of brain injury) and should be delayed sufficiently to enable full clearance of sedatives and any neurological recovery to occur – in most cases, prognostication is not reliable until after 72 h from cardiac arrest. The tests are categorised:

- clinical examination – GCS score, pupillary response to light, corneal reflex,
presence of seizures
• neurophysiological studies – somatosensory evoked potentials (SSEPs) and electroencephalography (EEG)
• biochemical markers – neuron-specific enolase (NSE) is the most commonly used
• imaging studies – brain CT and magnetic resonance imaging (MRI).

Clinical examination

Bilateral absence of pupillary light reflex at 72 h from ROSC predicts poor outcome with close to 0% FPR but the sensitivity is relatively low (about 19%); in other words, of those who eventually have a bad outcome, only 1 in 5 will have fixed pupils at 72 h. Similar performance has been documented for bilaterally absent corneal reflex.132,133

An absent or extensor motor response to pain at 72 h from ROSC has a high (about 75%) sensitivity for prediction of poor outcome, but the FPR is also high (about 27%). The high sensitivity of this sign enables it to be used to identify the population with poor neurological status needing prognostication. The corneal reflex and the motor response can be suppressed by sedatives or neuromuscular blocking drugs.77 When interference from residual sedation or paralysis is suspected, prolonging observation of these clinical signs beyond 72 h from ROSC is recommended, in order to minimise the risk of obtaining false positive results.

Myoclonus is a clinical phenomenon consisting of sudden, brief, involuntary jerks caused by muscular contractions or inhibitions. A prolonged period of continuous and generalised myoclonic jerks is commonly described as status myoclonus. Although there is no definitive consensus on the duration or frequency of myoclonic jerks required to qualify as status myoclonus, in prognostication studies in comatose survivors of cardiac arrest the minimum reported duration is 30 minutes.

While the presence of myoclonic jerks in comatose survivors of cardiac arrest is not consistently associated with poor outcome (FPR 9%), a status myoclonus starting within 48 h from ROSC is consistently associated with a poor outcome (FPR 0% [95% confidence interval (CI) 0–5%]; sensitivity 8–16%). However, several case reports of good neurological recovery despite an early-onset, prolonged and generalised myoclonus have been published. In some of these cases myoclonus persisted after awakening and evolved into a chronic action
myoclonus (the Lance-Adams syndrome). The exact time when recovery of consciousness occurred in these cases may have been masked by the myoclonus itself and by ongoing sedation. Patients with post-arrest status myoclonus should be evaluated off sedation whenever possible; in those patients, EEG recording can be useful to identify EEG signs of awareness and reactivity and to reveal a coexistent epileptiform activity.

While predictors of poor outcome based on clinical examination are inexpensive and easy to use, they cannot be concealed from the treating team and therefore their results may potentially influence clinical management and cause a self-fulfilling prophecy.

**Electrophysiology**

**Short-latency somatosensory evoked potentials (SSEPs)**

In post-arrest comatose patients, bilateral absence of the N20 SSEP wave predicts death or vegetative state (CPC 4–5) with high reliability (FPR 0–2% with upper 95% CI of about 4%). The few cases of false reports observed in large patient cohorts were due mainly to artefacts. SSEP recording requires appropriate skills and experience, and utmost care should be taken to avoid electrical interference from muscle artefacts or from the ICU environment. In most prognostication studies bilateral absence of N20 SSEP has been used as a criterion for deciding on withdrawal of life-sustaining treatment (WLST), with a consequent risk of self-fulfilling prophecy.

**Electroencephalography**

**Absence of EEG reactivity:** Background reactivity means that there is a change in the EEG in response to a loud noise or a noxious stimulus such as tracheal suction. Absence of EEG background reactivity predicts poor outcome with a FPR of 0–2% (upper 95% CI of about 7%). However, most of the prognostication studies on absent EEG reactivity after cardiac arrest are from the same group of investigators. Limitations of EEG reactivity include lack of a standardised stimulus and modest inter-rater agreement.

**Status epilepticus:** In TTM-treated patients, the presence of status epilepticus (SE) (i.e. a prolonged epileptiform activity), is almost invariably - but not always - followed by poor outcome (FPR 0–6%), especially in presence of an unreactive or
discontinuous EEG background.

**Burst-suppression:** Burst-suppression has recently been defined as more than 50% of the EEG record consisting of periods of EEG voltage <10µV, with alternating bursts. However, most of prognostication studies do not comply with this definition. In comatose survivors of cardiac arrest, burst-suppression is usually a transient finding. During the first 24–48 h after ROSC burst-suppression may be compatible with neurological recovery, while at ≥72 h from ROSC a persisting burst-suppression pattern is consistently associated with poor outcome.

Apart from its prognostic significance, recording of EEG, either continuous or intermittent, in comatose survivors of cardiac arrest both during TH and after rewarming is helpful to assess the level of consciousness – which may be masked by prolonged sedation, neuromuscular dysfunction or myoclonus – and to detect and treat non-convulsive seizures, which occur in about 25% of comatose survivors of cardiac arrest.

**Biomarkers**

NSE and S-100B are protein biomarkers that are released following injury to neurons and glial cells, respectively. Their blood values after cardiac arrest are likely to correlate with the extent of anoxic-ischaemic neurological injury and, therefore, with the severity of neurological outcome. Advantages of biomarkers over both EEG and clinical examination include quantitative results and likely independence from the effects of sedatives. Their main limitation as prognosticators is that it is difficult to find with a high degree of certainty a consistent threshold for identifying patients destined to a poor outcome. In fact, serum concentrations of biomarkers are per se continuous variables, which limits their applicability for predicting a dichotomous outcome, especially when a threshold for 0% FPR is desirable.

**Neuron-specific enolase (NSE)**

In TTM-treated patients the thresholds for 0% FPR varied between studies but were as high as 150 mcg L$^{-1}$ at 24 and 48 h, and up to 80 mcg L$^{-1}$ at 72 h. The main reasons for the observed variability in NSE thresholds include variation between different analysers, the presence of extra-neuronal sources of biomarkers (haemolysis and neuroendocrine tumours), and the incomplete knowledge of the kinetics of its blood concentrations in the first few days after ROSC. Limited evidence suggests that the discriminative value of NSE values at
48–72 h is higher than at 24 h. Increasing NSE values over time may have an additional value in predicting poor outcome.

**Imaging**

**Brain CT**

The main CT finding of global anoxic-ischaemic cerebral insult following cardiac arrest is cerebral oedema, which appears as a reduction in the depth of cerebral sulci (sulcal effacement) and an attenuation of the grey matter/white matter (GM/ WM) interface, due to a decreased density of the GM, which has been quantitatively measured as the ratio (GWR) between the GM and the WM densities. The GWR threshold for prediction of poor outcome with 0% FPR in prognostication studies ranged between 1.10 and 1.22. The methods for GWR calculation were inconsistent among studies and, in any case, quantitative measurements are rarely made in clinical practice in the UK.

**MRI**

Brain MRI is more sensitive than CT for detecting global anoxic-ischaemic brain injury caused by cardiac arrest; however, its use can be problematic in the most clinically unstable patients. MRI can reveal extensive changes when results of other predictors such as SSEP are normal. All studies on prognostication after cardiac arrest using imaging have a small sample size with a consequent low precision, and a very low quality of evidence. Most of those studies are retrospective, and brain CT or MRI had been requested at the discretion of the treating physician, which may have caused a selection bias and overestimated their performance.

**Suggested prognostication strategy**

A careful clinical neurological examination remains the foundation for prognostication of the comatose patient after cardiac arrest. Perform a thorough clinical examination daily to detect signs of neurological recovery such as purposeful movements or to identify a clinical picture suggesting that brain death has occurred.

The process of brain recovery following global post-anoxic injury is completed
within 72 h from arrest in most patients. However, in patients who have received sedatives ≤12 h before the 72 h post ROSC neurological assessment, the reliability of clinical examination may be reduced. Before decisive assessment is performed, major confounders must be excluded; apart from sedation and neuromuscular blockade, these include hypothermia, severe hypotension, hypoglycaemia, and metabolic and respiratory derangements. Suspend sedatives and neuromuscular blocking drugs for long enough to avoid interference with clinical examination. Short-acting drugs are preferred whenever possible. When residual sedation/paralysis is suspected, consider using antidotes to reverse the effects of these drugs.

The prognostication strategy algorithm (Figure 2) is applicable to all patients who remain comatose with an absent or extensor motor response to pain at ≥72 h from ROSC. Results of earlier prognostic tests are also considered at this time point.

Evaluate the most robust predictors first. These predictors have the highest specificity and precision (FPR <5% with 95% CIs <5% in patients treated with controlled temperature) and have been documented in >5 studies from at least three different groups of investigators. They include bilaterally absent pupillary reflexes at ≥72 h from ROSC and bilaterally absent SSEP N20 wave after rewarming (this last sign can be evaluated at ≥24 h from ROSC in patients who have not been treated with controlled temperature). Based on expert opinion, we suggest combining the absence of pupillary reflexes with those of corneal reflexes for predicting poor outcome at this time point. Ocular reflexes and SSEPs maintain their predictive value irrespective of target temperature.

If none of the signs above is present to predict a poor outcome, a group of less accurate predictors can be evaluated, but the degree of confidence in their prediction will be lower. These have FPR <5% but wider 95% CIs than the previous predictors, and/or their definition/threshold is inconsistent in prognostication studies. These predictors include the presence of early status myoclonus (within 48 h from ROSC), high values of serum NSE at 48–72 h after ROSC, an unreactive malignant EEG pattern (burst-suppression, status epilepticus) after rewarming, the presence of a marked reduction of the GWR or sulcal effacement on brain CT within 24 h after ROSC or the presence of diffuse ischaemic changes on brain MRI at 2–5 days after ROSC. Based on expert opinion, we suggest waiting at least 24 h after the first prognostication assessment and confirming unconsciousness with a Glasgow motor score of 1–2 before using this second set of predictors. We also suggest combining at least
two of these predictors for prognostication.

No specific NSE threshold for prediction of poor outcome with 0% FPR can be recommended at present. Ideally, every hospital laboratory assessing NSE should create its own normal values and cut-off levels based on the test kit used. Sampling at multiple time-points is recommended to detect trends in NSE levels and to reduce the risk of false positive results. Avoid haemolysis when sampling NSE.

Although the most robust predictors showed no false positives in most studies, none of them singularly predicts poor outcome with absolute certainty when the relevant comprehensive evidence is considered. Moreover, those predictors have often been used for WLST decisions, with the risk of a self-fulfilling prophecy. For this reason, we recommend that prognostication should be multimodal whenever possible, even in presence of one of these predictors. Apart from increasing safety, limited evidence also suggests that multimodal prognostication increases sensitivity.

When prolonged sedation and/or paralysis is necessary, for example, because of the need to treat severe respiratory insufficiency, we recommend postponing prognostication until a reliable clinical examination can be performed. Biomarkers, SSEP and imaging studies may play a role in this context, since they are insensitive to drug interference.

When dealing with an uncertain outcome, clinicians should consider prolonged observation. Absence of clinical improvement over time suggests a worse outcome. Although awakening has been described as late as 25 days after arrest, most survivors will recover consciousness within one week.
9. Rehabilitation
Although neurological outcome is considered to be good for the majority of cardiac arrest survivors, cognitive and emotional problems and fatigue are common. Long-term cognitive impairments are present in half of survivors. Memory is most frequently affected, followed by problems in attention and executive functioning (planning and organisation). The cognitive impairments can be severe, but are mostly mild. Mild cognitive problems are often not recognised by health care professionals and cannot be detected with standard outcome scales such as the Cerebral Performance Categories (CPC) or the Mini-Mental State Examination (MMSE). Emotional problems, including depression, anxiety and post-traumatic stress are also common. Both cognitive and emotional problems have significant impact and can affect a patient’s daily functioning, return to work and quality of life. There is some evidence that follow-up care and rehabilitation after hospital discharge can improve outcome after cardiac arrest.

10. Organ donation

Organ donation should be considered in those who have achieved ROSC and who fulfil criteria for death using neurological criteria. In those comatose patients in whom a decision is made to withdraw life-sustaining therapy, organ donation should be considered after circulatory death occurs.

Non-randomised studies have shown that graft survival at one year is similar from donors who have had CPR compared with donors who have not had CPR.

Organ retrieval from donation after circulatory death (DCD) donors is classified as controlled or uncontrolled. Controlled donation occurs after planned withdrawal of treatment following non-survivable injuries and illnesses. Uncontrolled donation describes donation from patients with unsuccessful CPR in whom a decision has been made that CPR should be stopped. Uncontrolled donation is not yet practised widely in the UK. Once death has been diagnosed, the assessment of which includes a pre-defined period of observation to ensure a spontaneous circulation does not return, organ preservation and retrieval takes place.

11. Screening for inherited disorders
Many sudden death victims have silent structural heart disease, most often coronary artery disease, but also primary arrhythmia syndromes, cardiomyopathies, familial hypercholesterolaemia and premature ischaemic heart disease. Screening for inherited disorders is crucial for primary prevention in relatives as it may enable preventive antiarrhythmic treatment and medical follow-up.\(^{154-156}\) This screening should be performed using clinical examination, electrophysiology and cardiac imaging in specialist centres. In selected cases, genetic mutations associated with inherited cardiac diseases should also be searched.\(^{157}\)

### 12. Cardiac arrest centres

There is wide variability in survival among hospitals caring for patients after resuscitation from cardiac arrest. Many studies have reported an association between survival to hospital discharge and transport to a cardiac arrest centre but there is inconsistency in the hospital factors that are most related to patient outcome. There is also inconsistency in the services that together define a cardiac arrest centre. Most experts agree that such a centre must have a cardiac catheterisation laboratory that is immediately accessible 24/7 and the facility to provide targeted temperature management. The availability of a neurology service that can provide neuroelectrophysiological monitoring EEG and investigations (e.g. EEG and SSEPs) is also essential.

There is indirect evidence that regional cardiac resuscitation systems of care improve outcome after ST elevation myocardial infarction (STEMI).\(^{158}\) The implication from all these data is that specialist cardiac arrest centres and systems of care may be effective.\(^{159-162}\) Despite the lack of high quality data to support implementation of cardiac arrest centres, it seems likely that post-cardiac arrest care in the UK will become increasingly regionalised.

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14. Accreditation of the 2015 Guidelines

NICE has accredited the process used by Resuscitation Council UK to produce its Guidelines development Process Manual. Accreditation is valid for 5 years from March 2015. More information on accreditation can be viewed at https://www.nice.org.uk/about/what-we-do/accreditation.

15. References


40.


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